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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,674	08/09/2001	Suzanne Cory	11686A	3390

7590 07/22/2004

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,674	CORY ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-20* is/are pending in the application.

4a) Of the above claim(s) *11-17,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 5/6/04 has been acknowledged.

Claims 6-10 and 18 *are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***703-872-9306****.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

This application contains claims 11-17 and 19-20 are drawn to an invention nonelected with traverse in the reply filed on 8/21/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 6-10 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Guastella (US 5789201, 1998; earlier filing date 02/23/1996).

Instant claims are drawn to an isolated polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9 or a polypeptide encoded by the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 having 47% or greater similarity. In addition the claims are drawn to an isolated poly peptide encoded by a nucleic acid capable of hybridizing to the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 under low stringency condition and have having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9.

Guastella teaches nucleotide sequences encoding a bcl-2 homolog (bcl-y), which matches 98.2% to SEQ ID N0: 6 and 95.9% to SEQ ID NO:8. The cited art further teaches amino acid sequences which matches 99.5% to the SEQ ID NO:7 and 99.3% to SEQ ID NO:9 (see PTO sequence search report). In addition the cited art teaches that a functional derivative of disclosed bcl-2 polypeptide may or may not contain post-translational modifications such as covalently linked carbohydrate, depending on the necessity of such modifications for the performance of a specific function (col.4, line 67-). The cited art further teaches that "functional derivative" is intended to include the "fragments," "variants," "analogues," or "chemical derivatives" of a molecule (col.5, lines 1-6). The cited art further teaches the manufacturing of recombinant bcl-y or variants thereof which clearly encompasses the pharmaceutical composition of claim 18, since amino acid sequence disclosed in the cited prior is only 99.5% and 99.3% identical to the claimed SEQ ID NO:7 and SEQ ID NO:9 respectively. Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 112

Claims 6-10 and 18 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record as set forth in the office action mailed on 11/03/03.

Response to arguments

The applicant argues that the law does not require a reduction to practice for the purpose of satisfying the written description requirement under 35 U.S.C. 112, first paragraph. The applicant argues that that the specification describes the sequences (i.e., the structure) and the biological function of two polypeptides that are representative of the claimed polypeptide genus, therefore the claimed polypeptides are adequately described in compliance with the written description requirement.

However, applicant's argument are found NOT persuasive because the scope of invention as claimed encompasses any and all variants of polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9. At best the specification only teaches isolated polypeptide (human and mouse bcl-w) comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification as filed fails to disclose any variant of human or mouse bcl-w explicitly or implicitly that have bcl-w like activity.

Applicant were referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only teaches the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification as filed fails to disclose any variant of that has the functional property of human or mouse bcl-w polypeptide explicitly or implicitly as putatively claimed herein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nucleic acid and/or amino acid variants (as claimed) has been defined only by a statement of function that broadly encompasses bcl-2 or bcl-w like activity, which conveyed no distinguishing information about the identity of the claimed nucleic acid or amino acid sequences, such as its relevant structural or physical characteristics. The variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of a bcl-2 like polypeptide. In addition 53% variation (47% identical) as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University

Park Press: Baltimore, MD, pp. 1-7, 1976). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 6-10 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polypeptides comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6), does not reasonably provide enablement for any variant or derivative of an isolated polypeptide (bcl-w) consisting of amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons of record as set forth in the office action mailed on 11/03/03.

Nature of Invention:

Invention relates to a polypeptide or variant thereof that belongs to bcl-2 family.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses an isolated polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9 or a polypeptide encoded by the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 having 47% or greater similarity. In addition the claims are drawn to an isolated poly peptide encoded by a nucleic acid capable of hybridizing to the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 under low stringency condition and have having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9. At best the specification only teaches isolated polypeptide (human and mouse bcl-w) comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6).

The specification as filed fails to disclose any variant of human or mouse bcl-w explicitly or implicitly that have bcl-w like activity.

State of Art and Predictability

The stat of the art at the time of filing teaches that Bcl-2 family proteins play a central role in apoptosis regulation. The Bcl-2 family comprises various members which have very diverse functions. For example in humans over 20 members of this family have been identified, including proteins that suppress (Bcl-2, Bcl-XL, Mcl-1, Bfl-1/A1, Bcl-W) and proteins that promote (Bax, Bak, Bok, Bad, Bid, Bik, Bim, Nip3, Nix) cell death. Bcl-2 family proteins contain at least one of four conserved regions, termed Bcl-2 homology (BH)1 domains. Most members of this family also contain a TM domain located near their carboxyl terminus that anchors them in intracellular membranes of mitochondria and other organelles. Many Bcl-2 family proteins are capable of physically interacting, forming homo- or heterodimers, and functioning as agonists or antagonists of each other. Specificity for interaction partners and tissue-specific patterns of expression combine to endow each mammalian Bcl-2 family protein with a unique physiological role *in vivo*, resulting for example in highly diverse phenotypes when members of this multigene family are individually knocked out in mice. Thus, a need exists to identify comprehensively the members of the Bcl-2 family and to elucidate their functional characteristics (Ke at al, J. Biol. Chem., 276(16):12481-12484, 2001). In instant case considering the scope of variation as claimed *(53% variation, which also encompasses conserved motifs)*, it is highly unpredictable that variants as claimed would have any bcl-2 like activity. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited variants are mere hypothetical scenarios, since no biological functions have been established for the claimed variants. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding

residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). In addition considering the applicants disclosure and the state of bc-2 family art it is highly unpredictable that one skill in the art would be able to use the variants as claimed as a pharmaceutical composition to treat any disease without undue experimentation. Therefore, applicant has not presented enablement commensurate in scope with the claims.

Response to arguments

The applicant argues that the specification provides adequate guidance that enables those skilled in the art to make and use the claimed polypeptides. The applicant argues that the specification teaches the isolation of the human bcl-w gene (SEQ ID NO: 6), the murine bcl-w gene (SEQ ID N0: 8), and the encoded polypeptides. The specifcation also shows that the human Bcl-w protein and the murine Bcl-w share about 90% similarity and are known to regulate cell survival. The applicant argues that in the light of the present teaching, those skilled in the art can isolate a nucleic acid molecule that either hybridizes to SEQ ID NO: 6 or 8, or encodes a protein that shares at least about 47% similarity to SEQ ID NO: 7 or 9, and determine whether the encoded protein enhances cell survival. The applicant concluded that the experimentation required for those skilled in the art to make and use the claimed polypeptide is not undue.

However, applicant's arguments are found NOT persuasive. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case screening of any and all natural and non-natural variants, wherein 53% of amino acid are added substituted and /or deleted in the disclosed SEQ ID NO:7 and 9 is not considered routine in the art. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 53% amino acids are added, deleted and/or substituted. **The number of possible scenario increase geometrically with increase in percent non-identity**. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to

make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed bcl-2 and/or bcl-w like-activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is

571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER